Supplemental Material

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Supplemental Document. Approach to determination of primary nephrotic syndrome and presumed etiology.

Adult patients were considered to have confirmed nephrotic syndrome if they demonstrated evidence of the following in their available electronic medical records.

1. Laboratory result indicating nephrotic range proteinuria defined as:
    a. Urine albumin-to creatinine ratio (ACR) >3500 ug/mg OR
    b. Urine protein-to-creatinine ratio (PCR) >3.5 mg/mg OR
    c. 24-hour urine protein excretion >3500 mg
2. Consistent duration of proteinuria
3. Other contributing diagnostic or supportive criteria, if available
    a. Presence of renal biopsy results (used to assign etiology)
    b. Reduced serum albumin level (<3.0 g/dL)
    c. Elevated cholesterol level (e.g., total cholesterol >300 mg/dL)

The following exclusion criteria were applied if identified during physician adjudication of medical records:

1. Multiple myeloma
2. Nephrotic range proteinuria without confirmation of diagnosed nephrotic syndrome by a treating physician
3. Nephrotic range proteinuria developing after one kidney removal and no available biopsy result in the remaining kidney
4. Concomitant biopsy results showing focal segmental glomerulosclerosis and diabetic nephropathy
5. Post-transplant nephrotic syndrome or nephrotic range proteinuria developing after kidney transplantation
6. Nephrotic range proteinuria during pregnancy and subsequently sub-nephrotic range proteinuria after completion of the pregnancy
7. Transient nephrotic range proteinuria with no biopsy, no documented nephrology consultation, and no clinical follow-up
8. Biopsy-proven lupus nephritis associated with diagnosed systemic lupus erythematosus
9. Nephrotic range proteinuria that is attributed to a condition other than the three designated etiologies for classifying primary nephrotic syndrome (i.e., diabetes mellitus, systemic lupus erythematosus, Wegener's syndrome, hepatitis C, etc.)

Approach to assigning presumed cause of nephrotic syndrome by physician adjudicator:

1. When available, use pathologist-based renal biopsy results that describe a specific etiology of nephrotic syndrome
2. When multiple listed causes were found in the EHR, the treating nephrologist-assigned diagnosis was used
3. When no biopsy was performed or a biopsy result was unavailable, all other relevant clinical data was used to assign a presumed cause, if available (e.g., treating nephrologist notes)
4. All assigned etiologies were considered "presumed" unless a definitive renal biopsy result or other diagnostic test was available.

Supplemental Table 1. Baseline characteristics among 907 adults with confirmed primary nephrotic syndrome stratified by focal segmental glomerulosclerosis, membranous nephropathy or minimal change disease identified between 1996-2012.

Characteristic	Focal Segmental Glomerulosclerosis (N=359)	Membranous Nephropathy (N=366)	Minimal Change Disease (N=182)
Demographics			
Mean (SD) age, yr	46.9 (16.7)	53.0 (16.2)	44.8 (16.4)
Women, n (%)	153 (42.6)	147 (40.2)	90 (49.5)
Self-reported race, n (%)			
White/European	142 (39.6)	163 (44.5)	70 (38.5)
Black/African American	75 (20.9)	38 (10.4)	18 (9.9)
Asian/Pacific Islander	54 (15.0)	64 (17.5)	48 (26.4)
Other	24 (6.7)	39 (10.7)	12 (6.6)
Unknown	64 (17.8)	62 (16.9)	34 (18.7)
Hispanic ethnicity, n (%)	72 (20.1)	69 (18.9)	35 (19.2)
Low household educational attainment, n (%)	96 (26.7)	89 (24.3)	41 (22.5)
Median household income < $35,000, n (%)	41 (11.4)	43 (11.7)	20 (11.0)
Current or former smoker, n (%)	82 (22.8)	82 (22.4)	34 (18.7)
Medical history, n (%)			
Myocardial infarction	6 (1.7)	3 (0.8)	1 (0.5)
Unstable angina	4 (1.1)	1 (0.3)	1 (0.5)
Heart failure	12 (3.3)	12 (3.3)	1 (0.5)
Ischemic stroke	3 (0.8)	2 (0.5)	0 (0.0)
Transient ischemic attack	4 (1.1)	4 (1.1)	0 (0.0)
Venous thromboembolism	0 (0.0)	2 (0.5)	1 (0.5)
Peripheral artery disease	5 (1.4)	2 (0.5)	1 (0.5)
Hypertension	173 (48.2)	145 (39.6)	50 (27.5)
Dyslipidemia	143 (39.8)	162 (44.3)	65 (35.7)
Chronic liver disease	8 (2.2)	2 (0.5)	3 (1.6)
Chronic lung disease	48 (13.4)	63 (17.2)	28 (15.4)
Hyperthyroidism	5 (1.4)	15 (4.1)	5 (2.7)
Hypothyroidism	40 (11.1)	48 (13.1)	28 (15.4)
Diagnosed dementia	0 (0.0)	1 (0.3)	2 (1.1)
Cancer	16 (4.5)	17 (4.6)	7 (3.8)
Cardiac procedure history, n (%)			

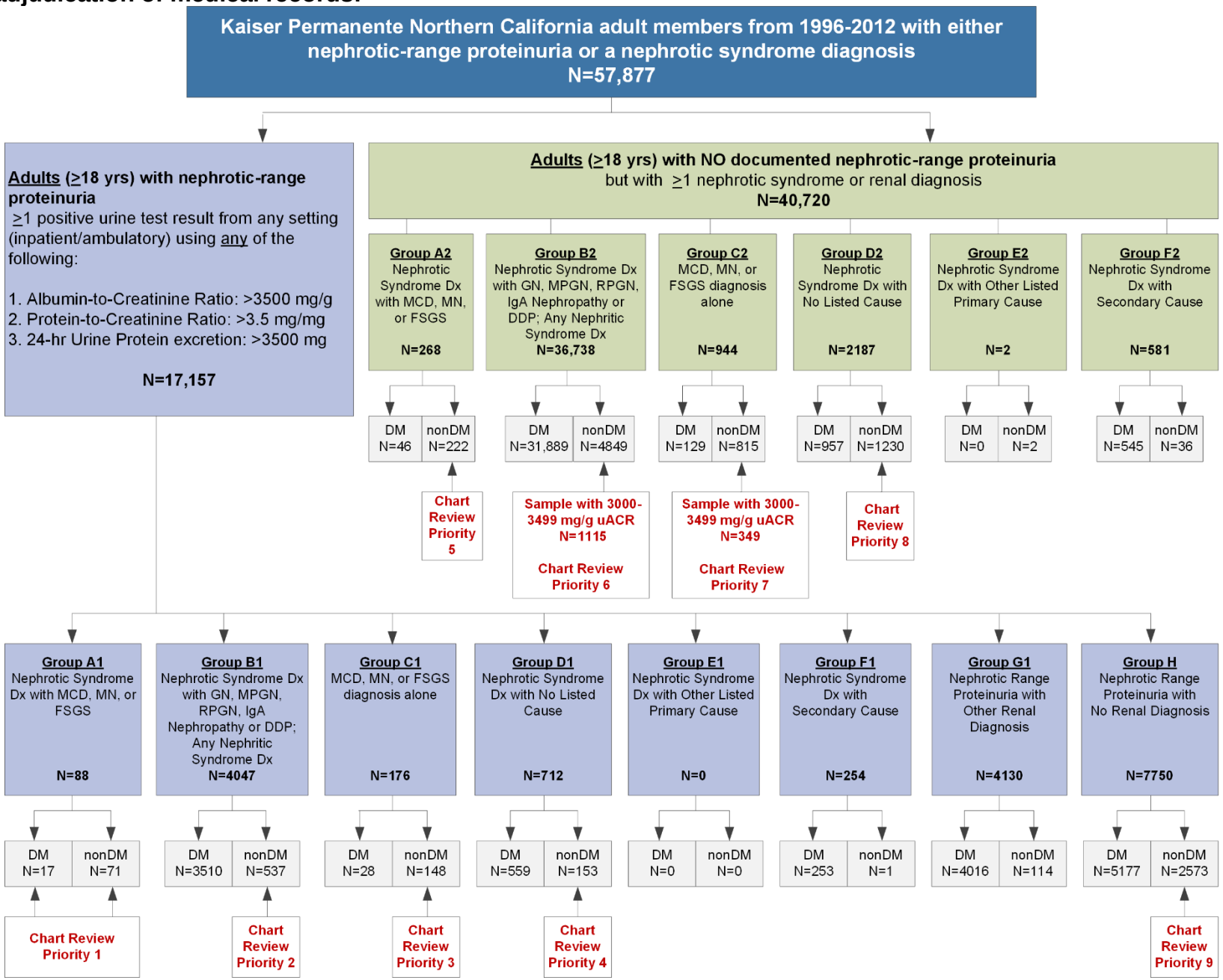
Characteristic	Focal Segmental Glomerulosclerosis (N=359)	Membranous Nephropathy (N=366)	Minimal Change Disease (N=182)
Coronary artery bypass graft surgery	4 (1.1)	0 (0.0)	1 (0.5)
Percutaneous coronary intervention	10 (2.8)	4 (1.1)	0 (0.0)
Medication use, n (%)			
ACE Inhibitors (ACEi)	90 (25.1)	103 (28.1)	36 (19.8)
Angiotensin II receptor blockers (ARB)	33 (9.2)	27 (7.4)	7 (3.8)
Beta-blocker	92 (25.6)	66 (18.0)	22 (12.1)
Calcium channel blocker	80 (22.3)	38 (10.4)	12 (6.6)
Diuretic	142 (39.6)	154 (42.1)	75 (41.2)
Any anti-hypertensive	214 (59.6)	216 (59.0)	92 (50.5)
Antiarrhythmic agent	0 (0.0)	0 (0.0)	1 (0.5)
Digoxin	5 (1.4)	3 (0.8)	1 (0.5)
Statin	85 (23.7)	105 (28.7)	34 (18.7)
Other lipid-lowering agent	16 (4.5)	15 (4.1)	4 (2.2)
Non-aspirin antiplatelet agent	12 (3.3)	8 (2.2)	0 (0.0)
Anticoagulant	7 (1.9)	2 (0.5)	1 (0.5)
Aldosterone receptor antagonist	6 (1.7)	5 (1.4)	2 (1.1)
Alpha blocker	37 (10.3)	26 (7.1)	9 (4.9)
Central ARA	21 (5.8)	10 (2.7)	5 (2.7)
Vital Signs			
Body mass index, kg/m^2, n (%)			
< 18.5	4 (1.1)	1 (0.3)	2 (1.1)
18.5-24.9	44 (12.3)	39 (10.7)	27 (14.8)
25.0-29.9	38 (10.6)	82 (22.4)	37 (20.3)
30.0-39.9	87 (24.2)	67 (18.3)	41 (22.5)
≥ 40.0	17 (4.7)	4 (1.1)	6 (3.3)
Unknown	169 (47.1)	173 (47.3)	69 (37.9)
Systolic blood pressure, mmHg, n (%)			
< 120	40 (11.1)	50 (13.7)	45 (24.7)
120-129	30 (8.4)	48 (13.1)	32 (17.6)
130-139	67 (18.7)	74 (20.2)	33 (18.1)
140-159	74 (20.6)	58 (15.8)	21 (11.5)
160-179	26 (7.2)	14 (3.8)	8 (4.4)
≥ 180	11 (3.1)	7 (1.9)	2 (1.1)
Unknown	111 (30.9)	115 (31.4)	41 (22.5)
Diastolic blood pressure, mmHg, n (%)			

Characteristic	Focal Segmental Glomerulosclerosis (N=359)	Membranous Nephropathy (N=366)	Minimal Change Disease (N=182)
≤ 80	124 (34.5)	160 (43.7)	88 (48.4)
81-84	30 (8.4)	21 (5.7)	20 (11.0)
85-89	32 (8.9)	33 (9.0)	18 (9.9)
90-99	35 (9.7)	24 (6.6)	10 (5.5)
100-109	17 (4.7)	9 (2.5)	3 (1.6)
≥ 110	10 (2.8)	3 (0.8)	2 (1.1)
Unknown	111 (30.9)	116 (31.7)	41 (22.5)
Laboratory values			
Estimated glomerular filtration rate, ml/min/1.73m^2			
90-150	66 (18.4)	124 (33.9)	78 (42.9)
60-89	43 (12.0)	93 (25.4)	40 (22.0)
45-59	49 (13.6)	35 (9.6)	22 (12.1)
30-44	57 (15.9)	43 (11.7)	12 (6.6)
15-29	76 (21.2)	26 (7.1)	4 (2.2)
< 15	27 (7.5)	9 (2.5)	1 (0.5)
Unknown	41 (11.4)	36 (9.8)	25 (13.7)
Serum albumin, mg/dL			
Mean (SD)	3.2 (0.9)	2.7 (0.8)	2.6 (0.9)
Median (IQR)	3.4 (2.4-3.9)	2.6 (2.1-3.3)	2.3 (1.9-3.3)
Missing, n (%)	161 (44.8)	145 (39.6)	75 (41.2)
Total cholesterol, mg/dL			
< 200	78 (21.7)	46 (12.6)	25 (13.7)
200-240	44 (12.3)	39 (10.7)	16 (8.8)
> 240	122 (34.0)	164 (44.8)	75 (41.2)
Unknown	115 (32.0)	117 (32.0)	66 (36.3)
Hemoglobin, g/dL			
< 9.0	5 (1.4)	6 (1.6)	0 (0.0)
9.0-9.9	9 (2.5)	10 (2.7)	3 (1.6)
10.0-10.9	27 (7.5)	15 (4.1)	2 (1.1)
11.0-11.9	36 (10.0)	34 (9.3)	8 (4.4)
12.0-12.9	52 (14.5)	41 (11.2)	14 (7.7)
≥ 13.0	162 (45.1)	187 (51.1)	111 (61.0)
Unknown	68 (18.9)	73 (19.9)	44 (24.2)

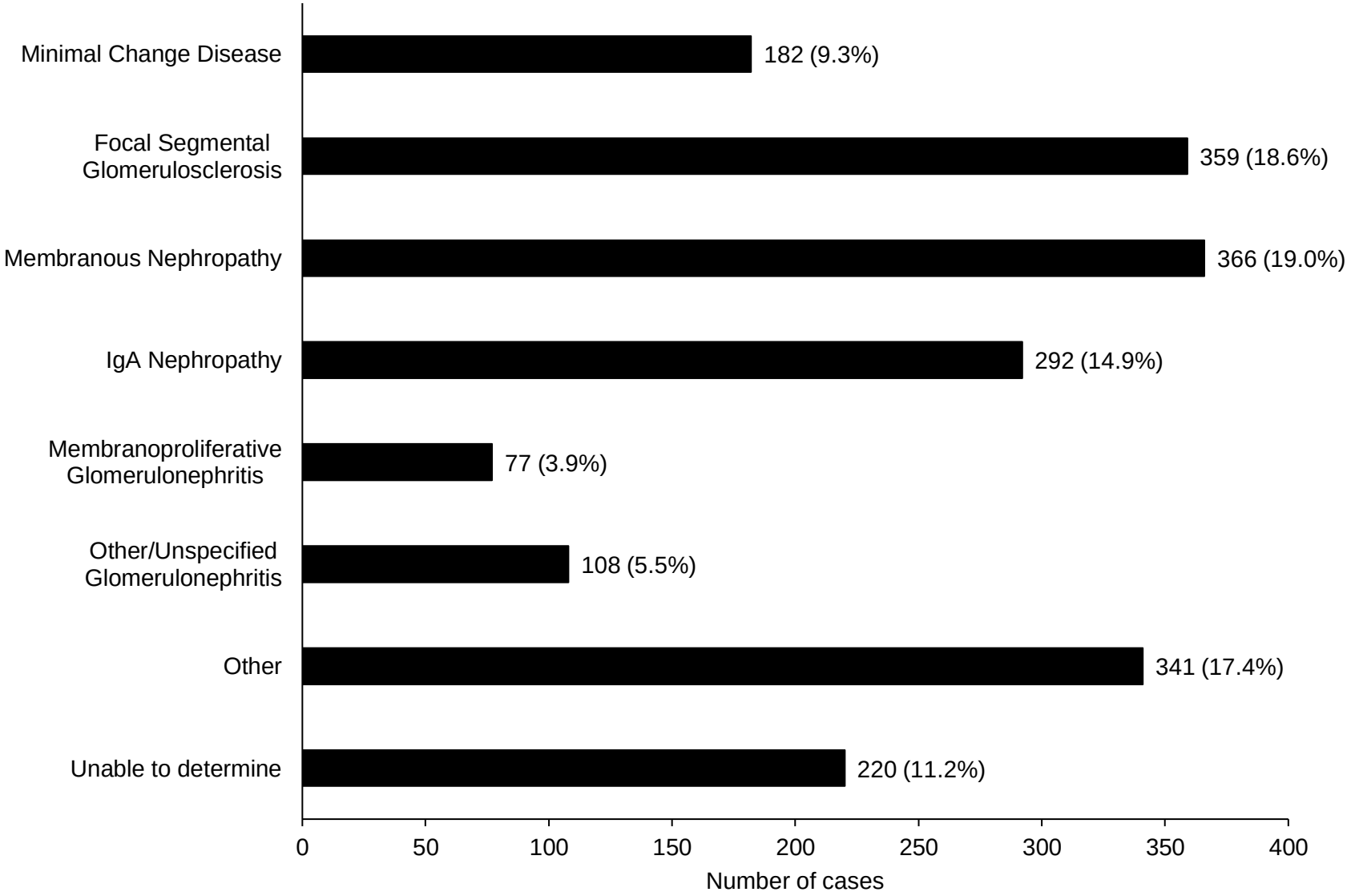
Supplemental Table 2. Multivariable association of primary nephrotic syndrome and subsequent ESKD with adjustment for time-updated comorbidities. All models adjusted for age, gender, race, ethnicity, smoking status, socioeconomic status, baseline comorbidities and laboratory values. Time-updated variables are age and comorbidities.

Comparison	Adjusted Hazard Ratio (95% Confidence Interval)
Primary nephrotic syndrome vs. no nephrotic syndrome	14.6 (9.6-22.3)
Minimal change disease vs. no nephrotic syndrome	4.1 (1.4-11.8)
Focal segmental glomerulosclerosis vs. no nephrotic syndrome	18.9 (11.5-31.0)
Membranous nephropathy vs. no nephrotic syndrome	15.5 (9.5-25.2)

Supplemental Figure 1. Prioritized subgroups of adults with potential nephrotic syndrome that underwent physician adjudication of medical records.

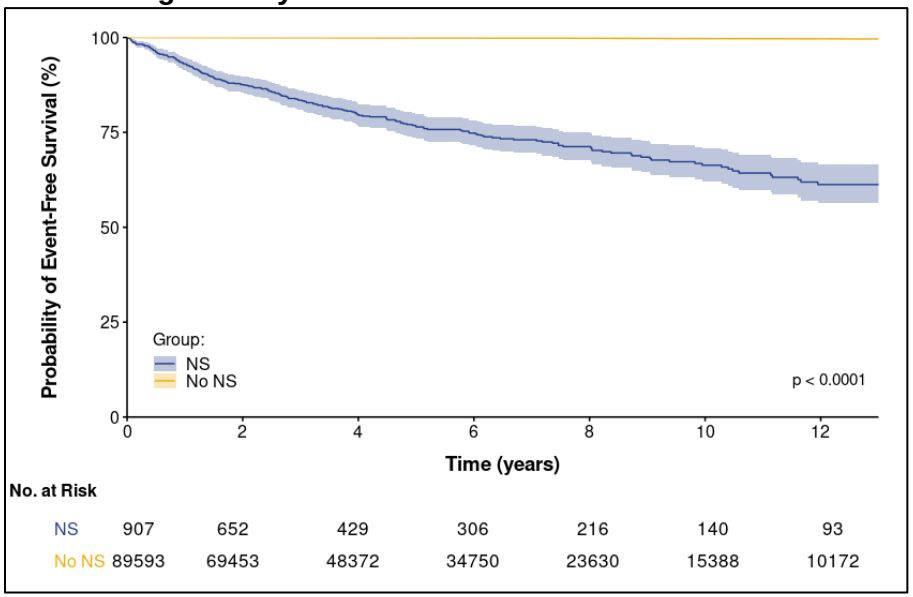


Supplemental Figure 2. Distribution of definite or presumed etiology in 1956 adults with confirmed nephrotic syndrome.

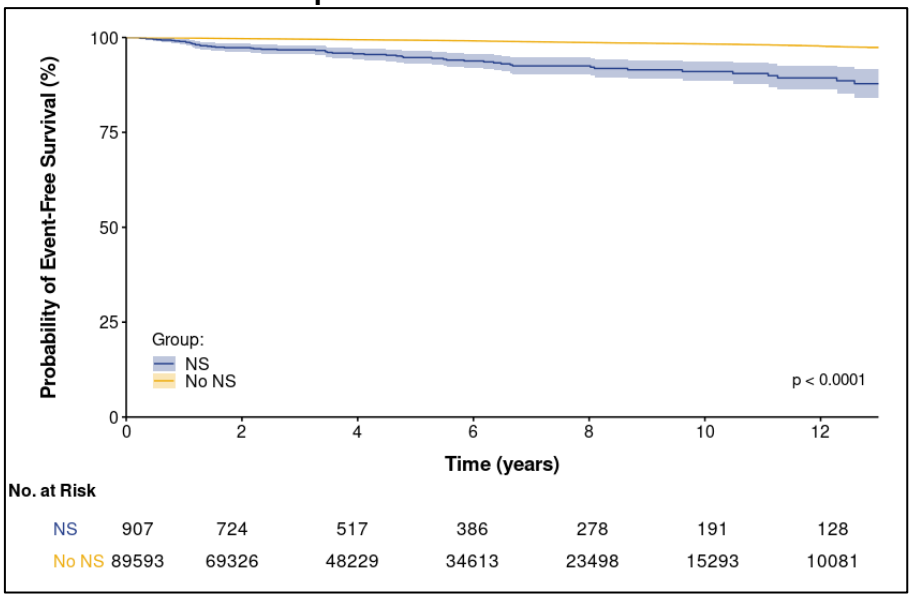


Supplemental Figure 3. Kaplan-Meier survival curves for clinical outcomes in adults with primary nephrotic syndrome vs. matched controls.

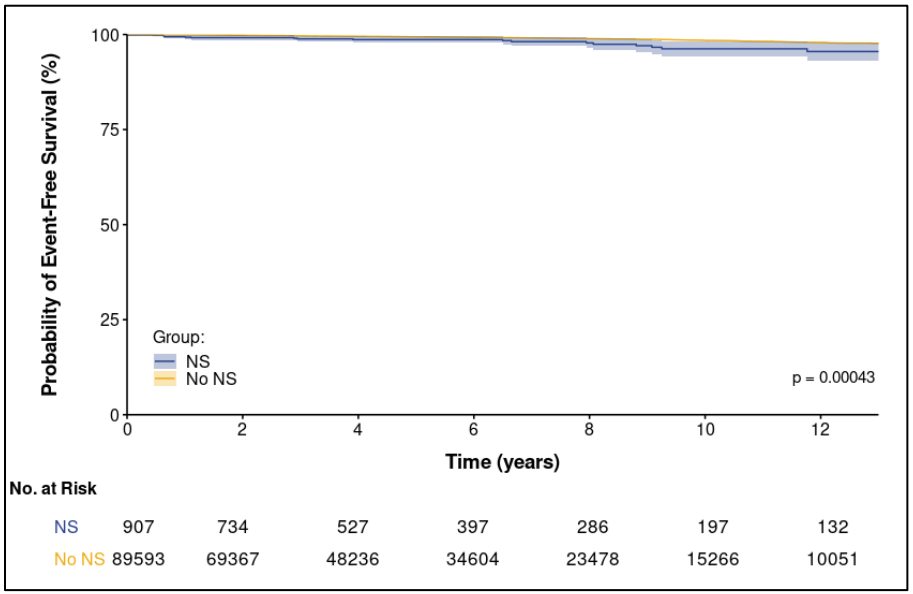
A. End-stage kidney disease



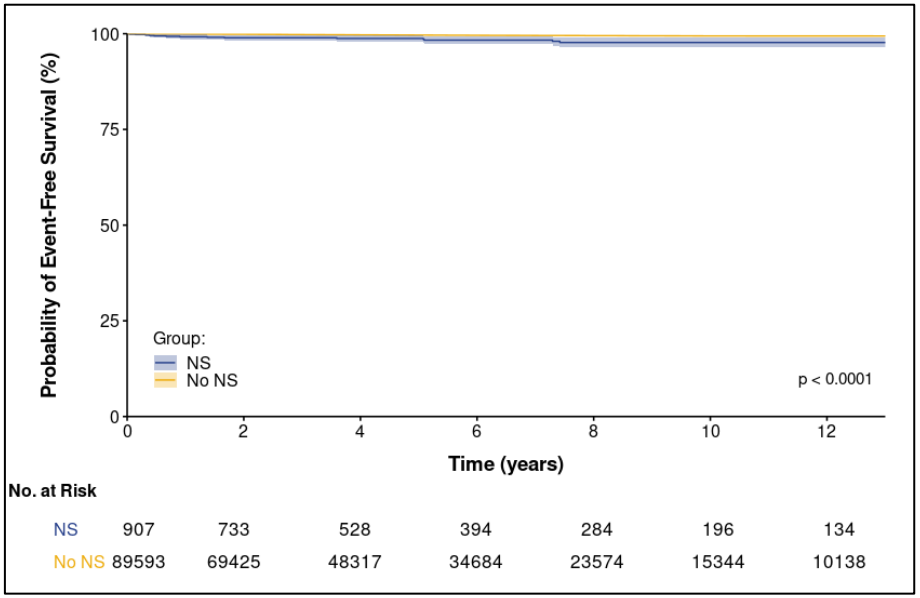
B. Heart failure hospitalization



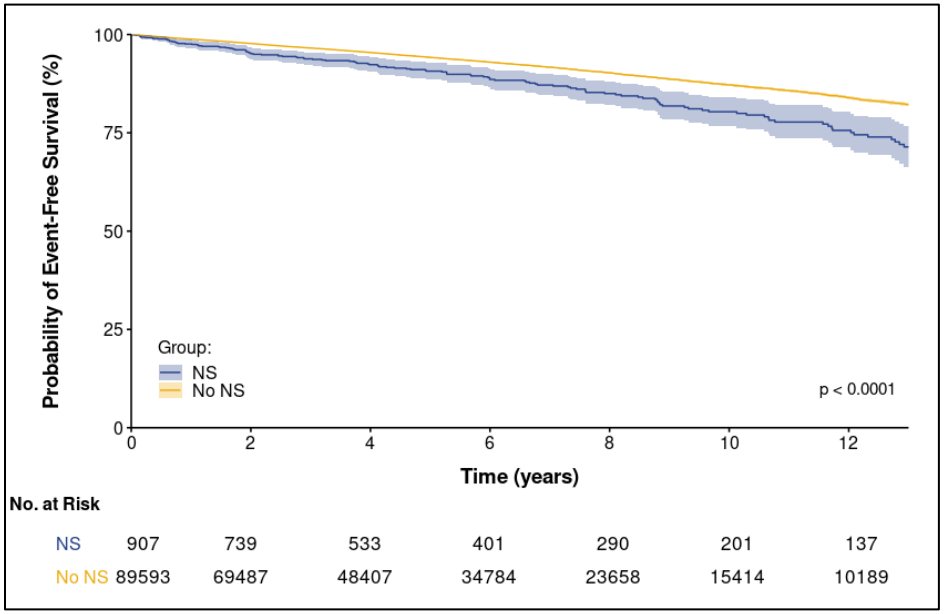
C. Stroke



D. Venous Thromboembolism



E. Death


Probability of Event-Free Survival (%)
100
75
50
25
0
Group:
NS
No NS
p < 0.0001
0
2
4
6
8
10
12
Time (years)
No. at Risk
NS 907 739 533 401 290 201 137
No NS 89593 69487 48407 34784 23658 15414 10189